Genetics inMedicine | CORRESPONDENCE

Fabry disease cardiac variant IVS4 +919 G>A is associated with multiple cardiac gene variants in patients with severe cardiomyopathy and fatal arrhythmia

To the Editor

We wish to respond to the recent *Genetics in Medicine* article on the endomyocardial biopsies of cardiac variant *GLA* IVS4+919A Fabry disease patients.[1] In the report, the authors have tried to emphasize the early initiation to prevent irreversible tissue damage in IVS4+919A individuals; however, they also noted the possibility of coincident conditions. The variant *GLA* IVS4+919A, with an allele frequency of 1/800 in Taiwanese males,[2] is occasionally associated with severe cardiomyopathy and cardiac arrhythmia. Nevertheless, the epidemiology doesn't support it as a significant variant in Fabry disease.[3] It is not known why only a small portion of patients carrying this variant are affected by clinically dangerous conditions. Though family screening, we even encountered one asymptomatic 92-year-old IVS4+919A male. We also met three IVS4+919A males, with mild elevation of plasma lysoGb3 (3.35–4.33 ng/mL, $N < 0.8$), presenting with severe complicated progressive cardiomyopathy, and fatal arrhythmia in two patients. Therefore we applied exome sequencing (ES), focusing on genes associated with either cardiomyopathy or arrhythmia, to these three patients, searching for an explanation for the phenotype heterogeneity.

Patient 1, a 59-year-old male index case, presented with asymmetrical and marked hypertrophy since the age of 50, followed by sick sinus syndrome (SSS). At the age of 55, he received pacemaker implantation (dual-chamber, rate-modulated pacing [DDDR]) for SSS with low ventricular rate. A myocardial biopsy revealed focal interstitial fibrosis, mild lymphocyte infiltration, periodic acid–Schiff (PAS)-positive cytoplasmic granules in the vacuoles, hypertrophy and degenerative changes of myocytes with pleomorphic and hyperchromatic nuclei, and marked cytoplasmic vacuolization containing fine granules. Enzyme replacement therapy (ERT) with agalsidase alfa 0.2 mg/kg/every other week was applied, but his condition deteriorated. Two years later, due to severe low ejection fraction (EF; 35%), he was referred to our hospital for heart transplantation evaluation. An endomyocardial biopsy revealed diffuse foamy change with large clear intracytoplasmic inclusion in myocardial cells, fibrotic changes, and myocardial cell degeneration. The DDDR pacemaker was upgraded to a cardiac resynchronization therapy defibrillator. His dyspnea improved slightly and his pro–brain natriuretic peptide (pro-BNP) levels decreased from 9762 to 1800 pg/mL (normal <125 pg/mL). ES revealed two rare variants with uncertain significance, including *SCN5A* c.4282G>T (p.A1428S) and *DTNA* c.383C>T (p.S128L). His elder brother, also carrying this IVS4+919A variant, presented with only mild cardiac hypertrophy. He did not receive an ES study.

Patient 2, a 69-year-old man, suffered from syncope, chest tightness, and left ventricular hypertrophy (LVH) diagnosed at the age of 60 years, with dilated left atrial size (4.8 cm). At age 67, one left ventricular apical thrombus (2.7 × 1.5 cm) was noted by echocardiography, but he refused to have thrombus removal operation. His electrocardiogram (ECG) showed prolonged PR interval (170 ms), wide QRS complex (166 ms), and LVH with repolarization abnormality. Several episodes of paroxysmal atrial fibrillation and polymorphic ventricular tachycardia occurred over the next two years and he then received an implantable cardioverter–defibrillator (ICD). At that time, cardiac magnetic resonance imaging (MRI) showed multiple patchy enhancement at all LV segments and global hypokinesia of LV. An endomyocardial biopsy showed central vacuolation, myofibrillar loss, and enlarged hyperchromatic nuclei of myocyte with interstitial fibrosis and disarray. He died two months later. ES revealed several rare variants with uncertain significance, including *GNB5* c.862C>T (p.R288W), *PLEC* c.1364C>T (p.A455V), *SGCD* c.717C>G (p.D239E), and *TCAP* c.458G>A (p.R153H). His daughter also carries the *TCAP* variant but had a normal ECG and MRI at the age of 39 years.

Patient 3, a 66-year-old male, has been diagnosed and under medical control for hypertensive cardiovascular disease, hypertension, and chronic bronchitis since the age of 56 years. At the age of 62, an ECG showed prolonged PR interval (158 ms), widened QRS complex (150 ms), and LVH with repolarization abnormality. Echocardiography showed concentric LVH, reduced ejection fraction (EF 53.7%), and frequent ventricular premature contraction (VPC). Over the next five years, he suffered from new coronary artery disease (one vessel), cholangiocarcinoma, chronic kidney disease, and transient ischemic stroke. At the age of 67, he developed paroxysmal atrial fibrillation with bifascicular bundle branch block (LBBB and LAFB). Cardiac MRI showed multiple patchy delayed enhancement of the LV walls especially RV insertion site and global hypokinesia of LV predominantly septal wall. An endocardial biopsy revealed diffuse intracytoplasmic vacuolization with scattered interstitial fibrosis. He died one month later. ES revealed several rare variants with uncertain significance, including *SCN5A* c.687T>C (p.T229T),

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ANK2 c.8240G>A (p.R2747H), *ABCC9* c.1988G>A (p.R663H), and *TTN* c.12977C>T (p.T4326I), c.14675G>A (p.R4892Q), c.42372C>G (p.D14124E), and c.46981G>A (p.V15661M).

This study illustrates the uncertainties that we face during clinical practice in diagnosing Fabry disease, especially now that genetic testing for Fabry disease and cardiomyopathy have become more widespread. Patients with nonclassic variants such as *GLA* N215S may have mild disease or even remain asymptomatic,[4] similarly to the individuals carrying *GLA* IVS4+919A variant. The natural history of such individuals is unknown. Therefore we have limited ability in counseling and management.

Through an ES approach, we demonstrate the possible influence of modifier genes and other factors on the severity of the disease phenotype. In our three patients, multiple rare variants, with mild to moderate severity defined as either one of the SIFT/PolyPhen-2 prediction being benign or the interpretation from ClinVar being conflicting or uncertain, were found in genes associated with cardiomyopathy or arrhythmia. Among them, the ion channel protein gene *SCN5A* (sodium channel) and *ABCC9* (potassium channel) are associated with Brugada syndrome, arrhythmia, and cardiomyopathy. That *SCN5A* variant itself could cause severe cardiac arrhythmia, not to mention the even worse outcome if it occurs simultaneously with a Gb3 accumulated heart. Similarly, a mild to moderate variant on the genes encoding proteins of the sarcomere (*TTN* and *TCAP*), cytoskeleton (*ANK2* and *PLEC*), and sarcoglycan (*SGCD* and *DTNA*) may additionally damage the cardiac tissue. Also, patient 3 had many comorbidities; all may contribute to his severe cardiomyopathy. Therefore, a multifactorial model, consisting of the combinations of multiple variants, in conjunction with other organ-related or environmental factors, may be a better explanation for this *GLA* IVS4+919A variant associated with cardiac manifestations. Consequently, a compiling of management strategies to decrease all risks, rather than a single treatment, is warranted to optimize the outcomes of these patients.

DISCLOSURE

The authors declare no conflicts of interest. This study was approved by the National Taiwan University Hospital Institutional Review Board (No. 201505135RINA).

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REFERENCES

1. Hsu MJ, Chang FP, Lu YH, et al. Identification of lysosomal and extralysosomal globotriaosylceramide (Gb3) accumulations before the occurrence of typical pathological changes in the endomyocardial biopsies of Fabry disease patients. Genet Med. 2018 Jun 6; https://doi.org/10.1038/s41436-018-0010-z [Epub ahead of print].
2. Chien YH, Lee NC, Chiang SC, Desnick RJ, Hwu WL. Fabry disease: incidence of the common later-onset alpha-galactosidase A IVS4+919G–>A mutation in Taiwanese newborns—superiority of DNA-based to enzyme-based newborn screening for common mutations. Mol Med. 2012;18:780–784.
3. Chiang HL, Wang NH, Song IW, et al. Genetic epidemiological study doesn't support GLA IVS4+919G>A variant is a significant mutation in Fabry disease. Mol Genet Metab. 2017;121:22–27.
4. Eng CM, Resnick-Silverman LA, Niehaus DJ, Astrin KH, Desnick RJ. Nature and frequency of mutations in the alpha-galactosidase A gene that cause Fabry disease. Am J Hum Genet. 1993;53:1186–1197.

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